Cumulative Absolute Breast Cancer Risk for Young Women Treated for Hodgkin Lymphoma

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Background: **Many women develop breast cancer after treatment for Hodgkin lymphoma (HL) at a young age. We estimated this future risk, taking into account age and calendar year of HL diagnosis, HL treatment information, population breast cancer incidence rates, and competing causes of death.** ***Methods:*** **Relative risks of breast cancer for categories defined by radiation dose to the chest (0, 20–<40 Gy, or ≥40 Gy) and use of alkylating agents (yes or no) were estimated from a case–control study conducted within an international population-based cohort of 3817 female 1-year survivors of HL diagnosed at age 30 years or younger from January 1, 1965, through December 31, 1994. To compute cumulative absolute risks of breast cancer, we used modified standardized incidence ratios to relate cohort breast cancer risks to those in the general population, enabling application of population-based breast cancer rates, and we allowed for competing risks by using population-based mortality rates in female HL survivors.** ***Results:*** **Cumulative absolute risks of breast cancer increased with age at end of follow-up, time since HL diagnosis, and radiation dose. For an HL survivor who was treated at age 25 years with a chest radiation dose of at least 40 Gy without alkylating agents, estimated cumulative absolute risks of breast cancer by age 35, 45, and 55 years were 1.4% (95% confidence interval [CI] = 0.9% to 2.1%), 11.1% (95% CI = 7.4% to 16.3%), and 29.0% (95% CI = 20.2% to 40.1%), respectively. Cumulative absolute risks were lower in women treated with alkylating agents.** ***Conclusions:*** **Breast cancer projections varied considerably by type of HL therapy, time since HL diagnosis, and age at end of follow-up. These estimates are applicable to HL survivors treated with regimens of the past and can be used to counsel such patients and plan management and preventive strategies. Projections should be used with caution, however, in patients treated with more recent approaches, including limited-field radiotherapy and/or ovary-sparing chemotherapy. [J Natl Cancer Inst 2005;97:1428–37]**

Advances in the treatment of Hodgkin lymphoma (HL) have resulted in a large number of long-term survivors at risk for the serious late effects of therapy, including the development of new malignant neoplasms *(1,2)*. Second cancers are currently the primary cause of mortality among these patients *(3,4)*, with breast cancer being the most common solid tumor among women *(1,5)*. The largest excesses of breast cancer are observed among women diagnosed with HL at age 30 years or younger *(6–10)*, a pattern that is consistent with the known radiosensitivity of the breast at young ages *(11)*. In a large international study *(12,13)*, elevated risks of breast cancer among young HL patients were strongly related to chest radiotherapy for HL, and risk increased up to eightfold with increasing radiation dose to the area of the breast in which cancer developed. This elevated radiation-related risk persisted for more than 25 years after treatment *(12)*, consistent with other studies showing that excess breast cancers after exposure to ionizing radiation may occur throughout life *(11)*.

Despite the concern over breast cancer risk among young women treated with chest radiotherapy for HL, individualized predictions of cumulative absolute risk, such as those that have been developed for women in the general population *(14)*, are not available for these HL survivors. Estimates of the cumulative incidence of breast cancer after treatment for HL at age 30 years or younger have been sparse, inconsistent, and series specific, ranging from 4.2% to 34% at 20–25 years of follow-up *(8,15–17)*. Moreover, most estimates have not taken into account the influence of competing causes of mortality *(18)*, which can be substantial among HL patients *(3,4,19,20)*, or the effect of alkylating agent therapy, which can lower subsequent breast cancer risk *(12,13)*. No study has attempted a comprehensive risk assessment that would be uniquely helpful for treated women and their physicians. Accurate projections of breast cancer risk are important for the development of

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risk-adapted long-term management strategies and for the assessment of disease burden among the growing population of HL survivors. Moreover, increasing patient and health care provider awareness of the high risk of breast cancer after therapy for HL generates a need for informed counseling of women treated at a young age *(21)*.

To enable more precise estimation of future breast cancer risk in HL survivors, we calculated the cumulative absolute risk of breast cancer among women treated for HL at age 30 years or younger, by use of measures of radiation dose and chemotherapy which are routinely available from medical records and which do not require specialized radiation dosimetry or chemical usage computation. We also took into account age and calendar year of HL diagnosis, age at counseling, baseline breast cancer incidence rates, and competing causes of mortality. The underlying analytic investigation *(12)* was based on the largest number (n = 105) of breast cancers reported to date among young women with HL.

Patients and Methods

Study Subjects

The study subjects included in the analysis have been previously described *(12)*. In brief, 3817 women who were treated for HL at age 30 years or younger between January 1, 1965, and December 31, 1994, and who survived for at least 1 year were identified in five population-based cancer registries in Iowa, Denmark, Finland, Sweden, and Ontario and the affiliated tumor registries of The Netherlands Cancer Institute, the Dr. Daniel den Hoed Cancer Center, Leiden University Medical Center, and the Catharina Hospital in The Netherlands *(13)*. The median (and also the mean) age at HL diagnosis of these women was 22 years, with 20% of the patients diagnosed between the ages of 13 and 17 years. A total of 105 women who had developed second primary breast cancers, including eight patients with ductal carcinoma in situ, were identified by record linkage within the respective cancer registries. Forty-one (39%) of the 105 breast cancers developed at least 20 years after HL diagnosis, and 14 (13%) of the 105 breast cancers developed at least 25 years after HL diagnosis. The median latency was 18 years (range = 7–30 years). Because the study end point was the initial diagnosis of breast cancer, data on subsequent breast tumors were not collected.

In a nested case–control study *(12)* that was undertaken to estimate the relative risk of breast cancer associated with HL treatments, each case patient with breast cancer was matched to at least two randomly selected control subjects. Matching factors were registry, calendar year of HL diagnosis, age at HL diagnosis, and length of survival without a second cancer at least as long as the interval between the diagnoses of HL and breast cancer in the case patient. For all 105 case patients and 266 control subjects, detailed data were collected regarding all treatments for HL, including daily radiotherapy logs that described tumor dose and fields and each chemotherapy drug, its amount, and method of administration. Of 360 women given therapeutic radiation among the 371 case patients and control subjects *(12)*, 292 (81.1%) received standard mantle radiotherapy that included mediastinal, axillary, and supraclavicular lymph node areas. Fifty-three (14.7%) of the 360 patients received mediastinal radiotherapy with or without supraclavicular or axillary fields, and 15 (4.2%) of the 360 patients were treated with other fields (e.g., supraclavicular, axillary, cervical, or subdiaphragmatic). Average mediastinal doses administered to case patients and control subjects were 38.9 Gy and 38.6 Gy, respectively. Among women who received alkylating agents (37 case patients and 133 control subjects), mechlorethamine and procarbazine with vincristine and prednisone (MOPP) were given to 31 case patients and 107 control subjects; fewer patients received combination chemotherapy that included cyclophosphamide (three case patients and 14 control subjects) or other alkylating agents (three case patients and 12 control subjects). Treatment with alkylating agent chemotherapy resulted in a 40% reduction in breast cancer risk *(12)*, consistent with the known ovarian toxicity associated with these cytotoxic drugs, MOPP in particular *(22,23)*. Reductions in breast cancer risk were also observed for combination chemotherapy that included cyclophosphamide (relative risk [RR] = 0.3, 95% CI = 0.1 to 0.9) or other alkylating agents (RR = 0.4, 95% CI = 0.1 to 1.5) and for pelvic radiation treatments that resulted in a dose of at least 5 Gy to the ovaries *(12)*.

Radiation and Chemotherapy

In our prior report *(12)*, breast cancer risk was quantified in terms of radiation dose to the area of the breast in which cancer subsequently developed and radiation dose to the ovary, measurements that require extensive dosimetry estimation techniques that are not readily available to either patients or clinicians. Thus, the current projections of absolute breast cancer risk are based on treatment information that is more likely to be retrievable from medical records (i.e., total radiation dose to the mediastinum and whether or not alkylating agent chemotherapy was administered). Because no case patient received a radiation dose of at least 5 Gy to the ovaries without also receiving alkylating agents, ovarian dose was not included in the model; moreover, patients and physicians would not be able to reconstruct this dose. Although initial multivariate statistical models included total tumor dose to the mediastinum and to supraclavicular and axillary areas, doses to the two latter areas contributed negligibly to the prediction of future breast cancer risk after the mediastinal dose was taken into account. Thus, to increase the statistical precision of the prediction model, mediastinal radiotherapy (which was given to 96% of women who received radiotherapy) served as the fundamental measure of chest exposure. Twelve, 170, and 163 women received doses of 20–29 Gy, 30–39 Gy, and at least 40 Gy, respectively. The highest administered total mediastinal dose was 67 Gy. No woman received less than a 20-Gy total mediastinal dose, although breast doses could be less than 20 Gy.

Final categories for the risk projection model consisted of three mediastinal radiation dose groups (none, 20–<40 Gy, and ≥40 Gy). The cut points were patterned after those used in prior studies *(6,30)*, although our data were too sparse to subdivide the 20–<40 Gy category (only two case patients in our study received <30 Gy). Thus, when we cross-classified by alkylating agent administration (yes or no), six treatment groups resulted (Table 1). Because the largest number of patients (38 case patients and 64 control subjects) received at least 40 Gy of mediastinal irradiation and no alkylating agents, this category was designated the reference group. For all 105 case patients and all but one of the 266

control subjects, information on alkylating agent therapy and total mediastinal radiation dose was available.

Statistical Analysis

To estimate breast cancer risk for women treated for HL, we first calculated relative risks within the case–control subject data; however, because almost all women received some treatment, such relative risks (i.e., internal relative risks) are not reflective of risk in relation to the general population. Thus, we next estimated breast cancer risk compared with that for the general population, by use of the number of breast cancer cases that would be expected from available breast cancer incidence rates in the population-based registries that contributed to the cohort. We refer to these as external relative risks. Finally, combining information on external relative risks with data on population breast cancer incidence rates from the Surveillance, Epidemiology, and End Results (SEER) Program and with SEER Program data on competing causes of death in HL survivors *(24)*, we estimated cumulative absolute risk of breast cancer, as described in detail below.

For the 105 case patients and 265 control subjects with complete treatment information, relative risks of breast cancer compared with the reference group were calculated by use of conditional logistic regression, with main effects for mediastinal dose (two indicator variables) and for alkylating agent chemotherapy (one indicator variable). These estimates of internal relative risks within the cohort are denoted as $\hat{r}_{1i}$, where $i = 1, 2, \ldots, 6$, for the six categories shown in Table 1, and where $i = 6$ is the reference category. To calculate the external relative risks of breast cancer for HL patients compared with the general population, we estimated the relative risk of breast cancer in the reference category compared with that of the general population. This relative risk, which is analogous to a standardized incidence ratio (SIR), was based on the 92 breast cancers that were reported from the registries described above, excluding case patients from Leiden University Medical Center and the Catharina Hospital, for which expected numbers of case patients were not available (seventh column, Table 1). To estimate the SIR, we let d_i be the proportion of all secondary breast cancer patients in category i. The proportion of subjects in our cohort in the reference category can be estimated by

$$\hat{p}_6 = d_6 / \sum_{i=1}^{6} d_i / \hat{r}_{1i}.$$

In this calculation, $\hat{r}_{1i}$ is the internal relative risk from conditional logistic regression, but d_i values are estimated from the 92 observed case patients described above. We estimated the external relative risk, w, that compares our reference category with the general population from the formula, $\hat{w} = O_6/(\hat{p}_6 E)$, where O_6 is the observed number of case patients in the reference category (category 6; n = 33) (Table 1) and E is the total expected number of case patients (i.e., 15.69 patients) based on ages in the included study cohorts and on the age-specific breast cancer incidence rates in the general populations corresponding to each of the contributing registries. The quantity $\hat{w}$ resembles an SIR except that we used a special factor, $\hat{p}_6$, to estimate the expected count in the reference category of our cohort. The external relative risk for exposure category i is then estimated as $\hat{r}_i = \hat{r}_{1i} \times \hat{w}$. Estimates of $\hat{r}_i$ and the corresponding confidence intervals are shown in Table 1. Note that $\hat{r}_6 = \hat{w}$, because $i = 6$ is the reference category.

To obtain confidence intervals for each r_i, we used a bootstrap procedure. In each bootstrap replication, we first determined the number of case patients in each category i by an independent Poisson count with the mean equal to the number of case patients in category i in the original data (fourth column, Table 1) for $i = 1, 2, \ldots, 6$. For each category i, we resampled the resulting number of matched case–control sets with replacement. We then computed $\hat{r}_{1i}$ from a conditional logistic regression model, eliminated case patients from Leiden University Medical Center and the Catharina Hospital to compute $\hat{w}$, and calculated $\hat{r}_i = \hat{r}_{1i} \times \hat{w}$. The 2.5th percentile and the 97.5th percentile of the bootstrap distribution of $\hat{r}_i$ based on 10 000 bootstrap repetitions were taken as upper and lower 95% confidence limits on r_i (Table 1).

If a parametric Poisson bootstrap replicate had no case patients in both categories $i = 1$ and $i = 4$ (see fourth column, Table 1), the relative risk for these categories would be estimated as zero unless an adjustment was applied. Thus, only for these bootstrap replicates, we proceeded as follows: because category $i = 4$ (no mediastinal radiation and no alkylating agents) resembles a sample from the general population, we replaced the observed zero case patients by the number of case patients expected from general population rates, namely

$$\hat{p}_4 E(105/92) = (0.0383)(15.69)(105/92) = 0.686.$$

The ratio (105/92) reflects the fact that all registries contribute to the 105 case patients (see fourth column, Table 1), whereas only 92 case patients contribute to estimation of the external relative risk (seventh column, Table 1). Likewise, the zero count in category $i = 1$ was replaced with $\hat{p}_1(\hat{r}_{11}/\hat{r}_{14})E = (0.0823)(0.0740/0.159)(15.69)(105/92) = 0.686$.

All breast cancer patient counts in bootstrap replications were multiplied by 1000 to produce integer numbers of case–control sets before estimating the internal relative risks with conditional logistic regression analysis. To calculate the external relative risk estimate, $\hat{w}$, however, the original case counts, including fractional case counts (e.g., 0.686), were used, as in the seventh column of Table 1. Otherwise, the bootstrap calculation for that replicate was unchanged.

To calculate the cumulative absolute risk of breast cancer from age t to a later age $t + \tau$ for a woman diagnosed at age a, coming to counseling without a previous breast cancer diagnosis at age t in treatment category i, we used the formula

$$\int_t^{t+\tau} \hat{r}_i(u;a) h_1(u) \exp\left[-\int_t^u \{\hat{r}_i(v;a) h_1(v) + h_2(v;a)\} dv\right] du, \qquad [1]$$

where $h_1(u)$ is the age-specific breast cancer incidence rate (including ductal carcinoma in situ) at age u in a woman in the general population, and $h_2(v;a)$ is the age-specific hazard at age v of dying from non–breast cancer causes among women in the general population diagnosed with HL at a previous age a. The time scale in Eq. 1 is age. In this equation, we set $\hat{r}_i = 1.0$, for the first 5 years after HL diagnosis but otherwise used values in Table 1; thus, in Eq. 1, $\hat{r}_i(u;a) = \hat{r}_i I(u - a > 5) + I(u - a \leq 5)$, where the function, I, is 1 if its argument is true and 0 otherwise. The hazard h_1 was obtained from incidence rates for invasive breast cancer (n = 74 093) and ductal carcinoma in situ (n = 13 061) (International Classification of Diseases for Oncology

[ICD-0] codes 8201, 8500, 8501, 8503, 8504, 8507, and 8522) *(25)* among 40 171 007 non-Hispanic white females of ages 10 years and older reported to nine population-based registries that participate in the SEER Program (SEER-9) from January 1, 1996, through December 31, 2000 *(24)*. These incidence rates are provided in Appendix Table 1 and include the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah and the metropolitan areas of Detroit, Atlanta, Seattle–Puget Sound, and San Francisco–Oakland, which cover approximately 10% of the U.S. population.

To estimate h_2, we used data on mortality rates after HL diagnosis at ages 13–29 years inclusive (excluding breast cancer deaths) for non-Hispanic white women in SEER-9 from January 1, 1973, through December 31, 2000. Estimates of mortality hazard rates according to time since HL diagnosis are specified by year of diagnosis and age at diagnosis in Appendix Table 2. Because women diagnosed with HL in the 1990s had limited follow-up data, we extrapolated their hazards from those in groups diagnosed earlier, as described in Appendix Table 2. To convert h_2 from the time scale of duration since HL diagnosis to the age scale in Eq. 1, we calculated the current age as age at HL diagnosis plus duration of follow-up. Equation 1 was simplified, as in Gail et al. *(14)*, under the assumptions that h_1 is constant on 5-year intervals and that h_2 is constant on yearly intervals. Confidence limits on absolute risk projections are obtained by substituting corresponding confidence limits on r_i in Eq. 1, because Eq. 1 is monotonic in r_i. All statistical tests were two-sided.

Results

Compared with patients who received at least 40 Gy of mediastinal radiotherapy and no alkylating agents, internal relative risks (Table 1) were lower for patients who received alkylating agent chemotherapy (internal RR = 0.47, 95% CI = 0.27 to 0.79) (e.g., $\hat{r}_{13} = 0.47$ compared with $\hat{r}_{16} = 1.0$) and lower for those who received either no mediastinal radiation (internal RR = 0.16, 95% CI = 0.04 to 0.72) or a dose of 20–<40 Gy (internal RR = 0.82, 95% CI = 0.47 to 1.43). The three-degree-of-freedom main effects model, which included alkylating agents, no mediastinal dose, and a mediastinal dose of 20–<40 Gy, fit the data very well in comparison with a saturated five-degree-of-freedom model that included interactions between alkylating agents and radiation dose effects (likelihood ratio chi-square, two-degrees-of-freedom = 0.763; $P = .68$).

The risk of breast cancer after HL was higher in most treatment categories than in the general population, as indicated by external relative risks, $\hat{r}_i$, in Table 1. For example, those patients receiving at least 40 Gy without alkylating agent chemotherapy had an external relative risk of $\hat{r}_6 = \hat{w} = 10.5$ (95% CI = 6.8 to 16.0), compared with that of the general population. Table 2 shows cumulative absolute risks of breast cancer after HL treatment by age at HL diagnosis, duration of follow-up, and age at end of risk projection period. The risks ranged from 0% to 39.6%. Breast cancer risk increased with increasing mediastinal dose and, within each dose level group, was higher among patients who did not receive alkylating agent chemotherapy than among those who did. Within treatment categories, risk of breast cancer increased with age at HL diagnosis and with duration of follow-up; these variables sum to the attained age, a major determinant of baseline breast cancer risk. For example, for HL patients diagnosed at age 15 years who received a mediastinal dose of at least 40 Gy and no alkylating agents, cumulative projected risks of breast cancer at 10, 20, and 30 years of follow-up (attained ages of 25, 35, and 45 years) were 0.1% (95% CI = 0 to 0.1), 1.7% (95% CI = 1.1 to 2.6), and 10.3% (95% CI = 6.8 to 15.2), respectively; corresponding estimates for a similarly treated woman diagnosed at age 25 years and followed for 10, 20, and 30 years (attained ages of 35, 45, and 55 years) were 1.4% (95% CI = 0.9 to 2.1), 11.1% (95% CI = 7.4 to 16.3), and 29.0% (95% CI = 20.2 to 40.1).

The risks for intervals not shown in Table 2 can be easily derived through linear interpolation; e.g., for the 25-year-old patient described above, risk of breast cancer over 25 years of

Table 1. Internal relative risks (RRs) [$\hat{r}_{1i}$] and external RRs [$\hat{r}_i$] of second primary breast cancer according to treatment in women diagnosed with Hodgkin lymphoma (HL) at age 30 years or younger*

Category number i	HL treatment†		No. of case patients for $\hat{r}_{1i}$ (n = 105)	No. of control subjects for $\hat{r}_{1i}$ (n = 265)	Internal RR[$\hat{r}_{1i}$]‡ (95% CI)	No. of case patients for $\hat{w}$ (n = 92)§	External RR[$\hat{r}_i$]‖ (95% CI)
	Mediastinal radiotherapy, Gy	Alkylating agents					
1	None	Yes	1	12	0.07 (0.02 to 0.36)	1	0.8 (0.3 to 2.6)
2	20–<40	Yes	23	73	0.38 (0.19 to 0.77)	21	4.0 (2.5 to 5.9)
3	≥40	Yes	13	48	0.47 (0.27 to 0.79)	13	4.9 (2.9 to 7.5)
4	None	No	1	11	0.16 (0.04 to 0.72)	1	1.7 (0.6 to 5.2)
5	20–<40	No	29	57	0.82 (0.47 to 1.43)	23	8.5 (5.4 to 13.2)
6¶	≥40	No	38	64	1.00 (reference)	33	10.5 (6.8 to 16.0)

*$\hat{r}_{1i}$ = estimated internal breast cancer relative risk comparing category i to category 6; $\hat{w}$ = external relative risk of breast cancer comparing a member of the HL cohort treated with at least 40 Gy but with no alkylating agents with a member of the general population; $\hat{r}_i = \hat{r}_{1i} \times \hat{w}$ = estimated external relative risk comparing a member of the HL cohort in category i with a member of the general population. Estimates include invasive breast cancer and ductal carcinoma in situ (DCIS), as in the underlying study *(12)*. CI = confidence interval; Gy = gray.

†Radiotherapy to the chest is expressed in terms of mediastinal dose. Alkylating agents consist largely of mechlorethamine and procarbazine.

‡Internal RR was fitted with a main effects model, including two indicator variables for mediastinal radiation dose and one indicator variable for alkylating agent therapy.

§Excludes 13 breast cancer cases from Leiden University Medical Center and the Catharina Hospital, Eindhoven, The Netherlands, because expected numbers of case patients were not available.

‖External RR was compared with invasive breast cancer and DCIS in the general population. External RR was obtained by multiplying the internal RR compared with the reference category ($i = 6$) by $\hat{w}$, which relates the reference category to the general population.

¶Reference category was chosen because it contains the largest number of case patients and control subjects.

Table 2. Cumulative absolute risks (%) of breast cancer for young women treated for Hodgkin lymphoma (HL) according to age at HL diagnosis, duration of follow-up (F), and treatment for HL*

Treatment for HL†		Cumulative absolute risk, % (95% CI)											
		Age 15 y at HL diagnosis			Age 20 y at HL diagnosis			Age 25 y at HL diagnosis			Age 30 y at HL diagnosis		
mRT	AA	10-y F	20-y F	30-y F	10-y F	20-y F	30-y F	10-y F	20-y F	30-y F	10-y F	20-y F	30-y F
None	Yes	0 (0 to 0)	0.1 (0.0 to 0.4)	0.8 (0.3 to 2.7)	0 (0 to 0.1)	0.4 (0.1 to 1.3)	1.6 (0.5 to 5.3)	0.1 (0.1 to 0.4)	0.9 (0.3 to 2.9)	2.6 (0.9 to 8.5)	0.4 (0.2 to 1.0)	1.8 (0.7 to 5.5)	4.0 (1.4 to 12.4)
20–<40 Gy	Yes	0 (0 to 0)	0.7 (0.4 to 1.0)	4.1 (2.6 to 5.9)	0.2 (0.1 to 0.2)	1.9 (1.2 to 2.8)	7.9 (5.0 to 11.4)	0.6 (0.4 to 0.8)	4.4 (2.8 to 6.4)	12.5 (8.0 to 17.8)	1.5 (1.0 to 2.1)	8.2 (5.2 to 11.8)	18.1 (11.8 to 25.3)
≥40 Gy	Yes	0 (0 to 0)	0.8 (0.5 to 1.2)	5.0 (3.0 to 7.5)	0.2 (0.1 to 0.3)	2.3 (1.4 to 3.5)	9.5 (5.8 to 14.3)	0.7 (0.4 to 1.0)	5.3 (3.2 to 8.1)	15.0 (9.3 to 22.1)	1.8 (1.1 to 2.6)	9.9 (6.1 to 14.8)	21.6 (13.6 to 30.9)
None	No	0 (0 to 0)	0.3 (0.1 to 0.8)	1.7 (0.6 to 5.3)	0.1 (0 to 0.2)	0.8 (0.3 to 2.5)	3.4 (1.3 to 10.1)	0.3 (0.1 to 0.7)	1.9 (0.7 to 5.7)	5.5 (2.1 to 15.9)	0.7 (0.3 to 1.9)	3.6 (1.4 to 10.5)	8.2 (3.2 to 22.7)
20–<40 Gy	No	0 (0 to 0.1)	1.4 (0.9 to 2.1)	8.5 (5.5 to 12.7)	0.3 (0.2 to 0.5)	4.0 (2.6 to 6.1)	16.0 (10.5 to 23.3)	1.1 (0.7 to 1.7)	9.1 (5.9 to 13.7)	24.6 (16.6 to 34.8)	3.0 (1.9 to 4.5)	16.6 (10.9 to 24.2)	34.1 (23.6 to 46.5)
≥40 Gy	No	0.1 (0 to 0.1)	1.7 (1.1 to 2.6)	10.3 (6.8 to 15.2)	0.4 (0.3 to 0.6)	4.9 (3.2 to 7.4)	19.1 (13.0 to 27.4)	1.4 (0.9 to 2.1)	11.1 (7.4 to 16.3)	29.0 (20.2 to 40.1)	3.6 (2.4 to 5.4)	19.8 (13.5 to 28.5)	39.6 (28.4 to 52.6)

*Includes invasive breast cancer and ductal carcinoma in situ. Risks for intervals not shown in the table can be derived through linear interpolation. The age at the end of risk projection period can be determined by adding the age at HL diagnosis and the duration of follow-up. AA = alkylating agents; CI = confidence interval; Gy = Gray; mRT = mediastinal radiotherapy.

†Radiotherapy to the chest is expressed in terms of mediastinal dose. Alkylating agents frequently included mechlorethamine and procarbazine; for women given chemotherapy regimens that confer minimal ovarian toxicity, projections of risk for women given radiotherapy alone may be more appropriate (refer to text).

Table 3. Cumulative absolute risks (%) of breast cancer for young women treated for Hodgkin lymphoma (HL) according to age at HL diagnosis, age at counseling, duration of follow-up after counseling, and treatment for HL*

Treatment for HL†		Cumulative absolute risk % (95% CI)											
		Age 15 y at HL diagnosis			Age 20 y at HL diagnosis			Age 25 y at HL diagnosis			Age 30 y at HL diagnosis		
mRT	AA	25 y/10 y‡	25 y/20 y	35 y/10 y	30 y/10 y	30y/20 y	40 y/10 y	35 y/10 y	35 y/20 y	45 y/10 y	40 y/10 y	40 y/20 y	50 y/10 y
None	Yes	0.1 (0 to 0.5)	0.9 (0.3 to 2.9)	0.8 (0.3 to 2.7)	0.4 (0.1 to 1.3)	1.7 (0.6 to 5.7)	1.5 (0.5 to 4.8)	0.8 (0.3 to 2.8)	2.7 (0.9 to 8.9)	2.1 (0.7 to 6.9)	1.5 (0.5 to 5.0)	3.9 (1.3 to 12.6)	2.7 (0.9 to 8.8)
20–<40 Gy	Yes	0.7 (0.4 to 1.0)	4.4 (2.8 to 6.5)	4.1 (2.6 to 6.0)	1.9 (1.2 to 2.8)	8.4 (5.3 to 12.2)	7.2 (4.6 to 10.5)	4.2 (2.6 to 6.2)	13.1 (8.4 to 18.7)	10.2 (6.5 to 14.7)	7.5 (4.7 to 10.8)	18.4 (11.9 to 25.9)	13.0 (8.3 to 18.6)
≥40 Gy	Yes	0.8 (0.5 to 1.3)	5.4 (3.2 to 8.2)	5.0 (3.0 to 7.6)	2.3 (1.4 to 3.6)	10.2 (6.2 to 15.3)	8.8 (5.3 to 13.3)	5.1 (3.1 to 7.8)	15.8 (9.8 to 23.3)	12.4 (7.6 to 18.4)	9.1 (5.5 to 13.7)	22.0 (13.8 to 31.8)	15.7 (9.7 to 23.2)
None	No	0.3 (0.1 to 0.9)	1.9 (0.7 to 5.7)	1.7 (0.6 to 5.3)	0.8 (0.3 to 2.5)	3.6 (1.3 to 10.8)	3.1 (1.1 to 9.3)	1.8 (0.7 to 5.5)	5.7 (2.1 to 16.7)	4.4 (1.6 to 13.1)	3.2 (1.2 to 9.6)	8.2 (3.1 to 23.2)	5.7 (2.1 to 16.6)
20–<40 Gy	No	1.5 (0.9 to 2.3)	9.2 (6.0 to 13.8)	8.6 (5.5 to 12.9)	4.0 (2.6 to 6.2)	17.1 (11.3 to 25.1)	14.9 (9.7 to 22.0)	8.8 (5.7 to 13.3)	25.9 (17.4 to 36.7)	20.6 (13.7 to 29.9)	15.3 (10.0 to 22.6)	35.1 (24.2 to 48.2)	25.8 (17.3 to 36.7)
≥40 Gy	No	1.8 (1.2 to 2.7)	11.1 (7.4 to 16.5)	10.4 (6.9 to 15.4)	4.9 (3.2 to 7.4)	20.5 (13.9 to 29.5)	17.9 (12.0 to 26.0)	10.7 (7.1 to 15.9)	30.6 (21.3 to 42.4)	24.6 (16.8 to 34.9)	18.4 (12.4 to 26.7)	40.9 (29.2 to 54.7)	30.5 (21.2 to 42.5)

*Includes invasive breast cancer and ductal carcinoma in situ. The age at the end of risk projection period can be determined by adding the age at counseling and the number of years of follow-up from the time of counseling. AA = alkylating agents; CI = confidence interval; Gy = gray; mRT = mediastinal radiotherapy.

†Radiotherapy to the chest is expressed in terms of mediastinal dose. Alkylating agents frequently included mechlorethamine and procarbazine, as described in the text.

‡Age at counseling/no. of years of follow-up from time of counseling.

follow-up would be intermediate between risks at 20 years and 30 years, namely (11.1%)(5/10) + (29.0%)(5/10) = 20.0%. We did not tabulate projections beyond 30 years of follow-up because our data do not extend that far. Breast cancer risks for a given age at diagnosis and follow-up time did not differ materially for women diagnosed with HL in the 1970s, 1980s, and 1990s and are not presented.

For patients who present for risk counseling several years after HL diagnosis, Table 3 can be used to estimate cumulative absolute breast cancer risks. For example, in Table 2, the 30-year risk of breast cancer for a woman diagnosed with HL at age 25 years with a mediastinal dose of at least 40 Gy and no alkylating agents is 29.0% (95% CI = 20.2 to 40.1). If, however, she presents for counseling at age 35 years, rather than at HL diagnosis, then her risk to age 55 years is 30.6% (95% CI = 21.3 to 42.4) (Table 3). The risk of breast cancer is smaller in the first case than in the second because the hazard of death is comparatively high in the first few years after HL diagnosis, which reduces the chance of developing breast cancer. Another apparent anomaly concerns two women diagnosed at the same age (e.g., 20 years), given the same treatment (e.g., a mediastinal dose of ≥40 Gy and no alkylating agents), and followed to the same attained age (e.g., 50 years) (Table 3). In this example, the woman counseled at age 30 years has a risk of 20.5% (95% CI = 13.9 to 29.5), whereas the woman counseled at age 40 years has a risk of 17.9% (95% CI = 12.0 to 26.0), because the former woman was followed and at risk of breast cancer during the ages of 30–40 years as well as during the ages of 40–50 years, whereas the latter woman was well at the time of counseling and, therefore, at risk only during the ages of 40–50 years.

Discussion

This study is the first, to our knowledge, to estimate the cumulative absolute risk of incident breast cancer among women treated for HL at age 30 years or younger from detailed information for radiation and chemotherapy. Our risk estimates derived from a large international population-based study *(12)*; projections take into account age and calendar year at HL diagnosis, time since treatment, and competing causes of mortality. Modified SIR calculations compare breast cancer risks in the HL cohort with general population risks, enabling the use of U.S. population-based age- and calendar year–specific breast cancer incidence rates. Mortality rates for competing risk calculations, stratified by calendar year period and age range at HL diagnosis, were similarly derived from U.S. population-based data. As expected, increasing age at HL diagnosis was associated with a higher cumulative absolute risk of breast cancer during follow-up after radiotherapy, reflecting the increase in background breast cancer incidence rates with age. It is sobering to realize that, by age 50 years, many of the women treated with high-dose chest radiotherapy had already exceeded the lifetime risk of developing breast cancer in the general population (in which one in eight women will develop breast cancer, or 13.4%) *(24)*.

Our results provide female HL patients with an estimate of therapy-related absolute breast cancer risk, particularly for those treated during the study period from January 1, 1965, through December 31, 1994. To date, no such type of systematic modeling has been undertaken for young women with HL, in contrast to the prediction tools available for women in the general population *(14,26–29)*. Compared with the general population, estimates of the relative risk of breast cancer in women after treatment for HL at age 30 years or younger have ranged from sixfold to 17-fold *(6–10)*, with the largest relative risks (60-fold to 112-fold) consistently being reported for patients treated at approximately age 16 years or younger *(7,10,17)*. The large variation in breast cancer relative risk estimates likely reflects differences in the proportion of irradiated patients, radiotherapy field size and dose, the use and type of alkylating agent chemotherapy, and the duration and completeness of follow-up. Because most relative risk estimates were derived from small numbers of breast cancers (median = 24 case patients; range = 14–32 among HL patients treated at age 30 years or younger) *(6–10)*, much of the variation may also be due to chance. Most of these series *(6–10)* also do not present breast cancer risks in relation to patient age and treatment parameters (i.e., radiotherapy fields and dose and use of alkylating agent chemotherapy), limiting comparisons with our results. From 25 breast cancers that occurred in women treated for HL at a mean age of 28 years (range = 4–81 years), Hancock et al. *(6)* noted that, compared with the general population, the relative risk of breast cancer after a mantle dose of 30–39 Gy or at least 40 Gy (with or without chemotherapy) was 3.7 (95% CI = 0.0 to 18.4) (one case patient) and 4.3 (95% CI = 2.6 to 6.1) (23 case patients), respectively; no breast cancers were reported after a dose of less than 30 Gy. Among children treated for HL before age 17 years who developed breast cancer (n = 17 patients), Bhatia et al. *(30)* found that mantle doses of 20–39 Gy and at least 40 Gy were associated with 5.9-fold (95% CI = 1.2-fold to 30-fold) and 23.3-fold (95% CI = 3.7-fold to 152-fold) overall relative risks of breast cancer, respectively, compared with a mantle dose of less than 20 Gy; risks were adjusted for alkylating agent chemotherapy, but separate estimates were not provided.

In most studies in which the absolute excess risk of breast cancer among women treated for HL at age 30 years or younger have been presented *(8,15,16)*, numbers of case patients are also small (range = 14–19 case patients), resulting in highly variable estimates, and competing risks are not considered. Two recent investigations *(17,31)* of breast cancer after childhood or adolescent HL, however, accounted for competing causes of death. Among girls treated with mantle radiotherapy for HL before age 17 years, the cumulative incidence of all invasive breast cancer (27 unilateral case patients plus 12 patients with contralateral tumors = 39) was 5.6% (95% CI = 2.8 to 8.3) and 16.9% (95% CI = 9.4 to 24.5%) at 20 and 30 years of follow-up, respectively *(17)*. Risks were not stratified by mantle dose (median = 36 Gy; range = 26–46 Gy) or by the administration of chemotherapy, although 50% of patients also received cytotoxic drugs. In a recent study by Kenney et al. *(31)*, 63 breast cancers developed in HL patients treated with chest radiotherapy before age 21 years. Although radiotherapy doses and fields were not described, the overall cumulative risk of breast cancer was 12.9% (95% CI = 9.3% to 16.5%) by age 40 years; estimates for other attained ages were not specified. In our model, a 20-year-old woman treated for HL with at least 40 Gy of mediastinal radiotherapy and no alkylating agents has a smaller cumulative absolute risk of breast cancer, i.e., 4.9% (95% CI = 3.2% to 7.4%) by age 40 years.

To provide perspective on the absolute risks presented in Tables 2 and 3, we draw comparisons to risks in the general SEER Program population and to risks in carriers of BRCA mutations. The absolute risks of breast cancer in white women from age 20 years to ages 30, 40, 50, and 60 years are, respectively, 0.04%, 0.5%, 2.0%, and 4.3%. These risks are calculated by using general population SEER Program rates for breast cancer [see Appendix Table 1 *(32)*] and national rates for competing causes of mortality. These risks were substantially lower than those in our Tables 2 and 3 for HL patients exposed to mediastinal radiation. Risks to age 60 years in BRCA1 and BRCA2 carriers were slightly more than 50% in several studies *(33)*, but lower values have been reported, including an estimate of 31% in a population-based study in Australia by Hopper et al. *(34)*. These values are not corrected for competing causes of mortality and are thus slightly larger than comparable estimates of absolute risk in Tables 2 and 3. Such data indicate that young women with HL who are treated with mediastinal radiation and who do not receive alkylating agents have risks comparable to or only modestly smaller than those of carriers of BRCA mutations.

The projections in Table 2 are subject to random and systematic errors. Although this study is based on the largest number of breast cancers to date in young women treated for HL, only 105 case patients were available, a limitation reflected in the wide confidence intervals. However, the bootstrap procedures used to produce confidence intervals account for the major sources of random variation, including the external relative risk estimation. The mortality rates from competing risks are assumed to be known with negligible random error. Sources of potential systematic error include the assumption that relative risks of breast cancer associated with HL radiotherapy are homogeneous across the ages at HL diagnosis of 15–30 years, an assumption that is consistent with our prior findings *(12)*. However, several reports from population-based cohort studies *(1,15)* and institutional series *(10,17)* suggest that HL patients treated before age 20 years may be at higher relative risk of breast cancer than older patients. Thus, we may have underestimated the absolute risks in women younger than 20 years. Data from non-HL cohorts have also indicated higher excess relative risks associated with breast radiation at younger ages *(11)*.

Another limitation of our study is that we were not able to include several established breast cancer risk factors in the prediction model, because the underlying study *(12)* did not contain sufficient detail for these variables. For example, a family history of two or more affected first-degree relatives may confer a twofold or larger elevated risk *(35)*, and women with atypical hyperplasia *(36)* or high mammographic density *(37)* have been reported to have a threefold to fivefold excess risk of breast cancer. Other breast cancer risk factors, such as age at menarche, age at first live birth, and use of hormone replacement therapy *(14,26,27,29)*, confer considerably lower risks. One approach to the evaluation of an HL patient with other breast cancer risk factors would be to multiply the treatment-associated relative risks in Table 1 by the relative risks estimated from separate studies for these influences and then recalculate Eq. 1 with the modified relative risks. The relative risk for the combined risk factors in the Gail model *(14)* can be approximated by the ratio of the 5-year absolute risk estimate from this model to the 5-year absolute risk for a woman with none of those risk factors; these two estimates can be obtained by running the risk prediction program at http://bcra.nci.nih.gov/brc/start.htm twice. A crude approximation to adjust for risk factors in the Gail model would then be to multiply the results in Table 2 by the ratio of these two estimates. This calculation assumes that there are no interactions on a multiplicative scale between these factors and radiation or chemotherapy for HL. Because little is known regarding the nature of such interactions, however, risk estimates obtained in this way are very uncertain.

Although our breast cancer estimates are appropriate for most women managed with HL treatment modalities used through the mid-1990s in our study *(12)*, considerable caution is needed in applying the results of Tables 2 and 3 to patients given later generations of treatment. Newer combination chemotherapy protocols (such as doxorubicin, bleomycin, vincristine, and dacarbazine) confer minimal ovarian toxicity *(38,39)*, in contrast to the established ovarian suppression that is associated with MOPP chemotherapy *(22,23)*. The observed reduction in breast cancer risk associated with MOPP and other alkylating agent–based regimens in the underlying study *(12,13)* was due largely, although not entirely, to the induction of premature menopause. Thus, for women treated with ovary-sparing chemotherapy regimens, estimates in Tables 2 and 3 that correspond to no alkylating agents might be more appropriate. In the past few years, radiotherapy techniques for HL have been refined to incorporate smaller fields *(40)* and to use lower doses (range = 20–30 Gy) *(41)*. These modifications result in exposure of smaller breast volumes to lower radiation doses and are expected to result in reduced risks of breast cancer in the future *(12,13)*. Our projections are largely based on women who received extended-field mantle radiotherapy, although radiation to other chest fields did not add statistically significantly to a risk model that included mediastinal dose. We were unable to reconstruct the proportion of breast tissue included in various radiotherapy fields *(12)*, and these types of dosimetric data would not be routinely available to patients or clinicians. Our estimates should be used cautiously for patients treated more recently with limited-field radiotherapy. Long-term studies are needed to assess breast cancer risk in such populations.

Our projections are most applicable to U.S. women, because they are based in part on breast cancer incidence rates reported to the National Cancer Institute's SEER Program, which enabled us to take into account both invasive breast cancer and ductal carcinoma in situ, as in the underlying study *(12)*. For countries with incidence rates of breast cancer lower than that of the U.S., the cumulative absolute risk of breast cancer after HL would correspondingly be lower. For example, if Swedish rates (which include only invasive breast cancer) are used *(42)*, the projected cumulative risks of breast cancer at 20 and 30 years of follow-up for a 25-year-old HL patient given a mediastinal dose of at least 40 Gy and no alkylating agents are 7.7% and 21.5%, respectively. If Dutch incidence rates for invasive breast cancer are used, the corresponding projected cumulative risks are 9.4% and 24.3%, similar to projections based on SEER Program rates limited to invasive breast cancer (i.e., 9.3% and 24.7%, respectively). All of these risks are somewhat smaller than the values 11.1% and 29.0% in Table 2, which includes U.S. rates for invasive breast cancer and ductal carcinoma in situ.

Absolute risk projections have value in counseling HL survivors and in developing clinical management strategies, including approaches to breast cancer screening and prevention *(43)*. HL survivors should be encouraged to retain treatment records. These data serve several purposes, such as facilitating risk projections, providing important information for clinical or therapeutic decisions with regard to future illness, and providing a basis for research into the long-term consequences of HL treatment. In any evaluation of the late effects of HL therapy, however, it should always be noted that the gains in long-term survival provided by successful radiotherapy and chemotherapy outweigh the associated risks of breast cancer and other late sequelae. Moreover, current modifications in treatment will likely result in lower risks of breast cancer in the future. In the interim, our projections of cumulative absolute risk of breast cancer associated with chest radiotherapy and alkylating agent chemotherapy serve as a unique and valuable resource for the large number of current HL survivors given therapeutic regimens of the past and can provide some perspective on risk for patients treated more recently.

Appendix Table 1. Age-specific breast cancer incidence rates (h_1) (per 100 000 female person–years) among non-Hispanic, white women reported to nine population-based cancer registries participating in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program (1996–2000)*

Age group	Incidence rate of breast cancer
10–14 y	0
15–19 y	0
20–24 y	1
25–29 y	8
30–34 y	27
35–39 y	69
40–44 y	143
45–49 y	236
50–54 y	319
55–59 y	400
60–64 y	457
65–69 y	516
70–74 y	562
75–79 y	579
80–84 y	536
85–89 y	437

*Includes invasive breast cancer and ductal carcinoma in situ (International Classification of Diseases for Oncology [ICD-0] codes 8201, 8500, 8501, 8503, 8504, 8507, 8522) *(25)*. Cancer registries include the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah and the metropolitan areas of Detroit, Atlanta, Seattle–Puget Sound and San Francisco–Oakland (SEER-9) *(24)*.

Appendix Table 2. Mortality hazard rates (h_2) for non–breast cancer deaths after Hodgkin lymphoma (HL) in non-Hispanic, white females reported to nine population-based cancer registries that participate in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program according to calendar year period, age at HL diagnosis, and time since HL diagnosis*

Time since HL diagnosis	Mortality hazard rates per 100 000 female person–years (h_2)					
	1973–1979		1980–1989		1990–2000	
	13–24 y/501 (127)†	25–29 y/214 (68)	13–24/786 (117)	25–29 y/425 (80)	13–24 y/700 (41)	25–29 y/407 (21)
1 y	2550	2550	2170	2170	816	816
2 y	2916	2916	2493	2493	1496	1496
3 y	2551	2551	2568	2568	1254	1254
4 y	2469	2469	1277	1277	1028	1028
5 y	1920	1920	833	833	752	752
6 y	1961	1961	1695	1695	910	910
7 y	834	834	580	580	1127	1127
8 y	2389	2389	689	689	578	578
9 y	1051	1051	1008	1008	778	778
10 y	1426	1426	206	206	0	0
11 y	1463	1463	1278	1278	0	0
12 y	186	186	671	671	671	671
13 y	943	943	770	770	770	770
14 y	765	765	752	752	752	752
15 y	784	784	543	543	543	543
16 y	797	797	883	883	883	883
17 y	613	613	1443	1443	1443	1443
18 y	631	631	775	775	775	775
19 y	1088	1088	1626	1626	1626	1626
20 y	1010	1881	1010	1881	1010	1881
21 y	873	2198	873	2198	873	2198
22 y	676	905	676	905	676	905
23 y	1237	3077	1237	3077	1237	3077
24 y	1031	0	1031	0	1031	0
25 y	2166	1980	2166	1980	2166	1980
26 y	0	2598	0	2598	0	2598
27 y	3637	0	3637	0	3637	0
28 y	1329	1580	1329	1580	1329	1580
29 y	1329	1580	1329	1580	1329	1580
30 y	1329	1580	1329	1580	1329	1580

*Cancer registries include the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah and the metropolitan areas of Detroit, Atlanta, Seattle–Puget Sound and San Francisco–Oakland (SEER-9) *(24)*. Mortality hazard rates are expressed per 100 000 female person–years. For calendar year period 1973–79, data on females 13–29 years of age at HL diagnosis were pooled and included in years 1–18 since HL diagnosis; for the years 19–26 since HL diagnosis, females 13–24 years of age at HL diagnosis were pooled, and females 25–29 years of age at HL diagnosis were analyzed separately; for years 27–29 since HL diagnosis, the average hazard rate from years 19–26 was used. For calendar period 1980–89, data on females 13–29 years of age at HL diagnosis were pooled and included in years 1–18 since HL diagnosis; mortality hazards for females 19–29 years since diagnosis were the same as for those in the 1973–79 calendar year period. For calendar period 1990–2000, data on females 13–29 years of age at HL diagnosis were pooled to estimate hazards for years 1–10 since HL diagnosis; for years 11–29 since HL diagnosis, the same hazard rates as for the 1980–89 calendar year period were used. Some erratic rates (e.g., 0) reflect small numbers of females at risk and small numbers of events in one-year intervals since HL diagnosis. The integration procedure (see Eq. 1) evens out erratic estimates. no. = number.

†Age at HL diagnosis/number of patients (number of deaths).

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Notes

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